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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,375	03/05/2002	Lawrence C. Smith	1051-1-020	6403

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KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,375	SMITH ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed November 26, 2004 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-18 and 20-38 are pending and subject to the examination below.

Applicant's amendment to claims 25-27 has overcome the rejection made in the office action mailed June 23, 2004 under 35 U.S.C. 101.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 and 28-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of preparing a reconstructed nonprimate mammalian oocyte, a method of reconstituting a nonprimate mammalian embryo, methods for production of a transgenic nonprimate mammalian embryo and methods of cloning a nonprimate mammal, where the donor cell, the oocyte and the surrogate mother are all of the same species, does not reasonably provide enablement for cross-species nuclear transfer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At the time of filing, the skilled artisan would have regarded the cloned primates as unpredictable. Pennisi cites several scientists working in the area of mammalian cloning who point to a lack of general and reproducible success, thus, emphasizing the lack of predictability at the time of filing. Robert Wall of the USDA is quoted as stating that despite years of effort, "[w]e're in the same bind that we've always been in. A majority of [would be clones] do not make it to term." (Pennisi and Vogel (2000), page 1722, col. 1, parag. 2, lines 9-14). Pennisi and Vogel state that "even when an embryo does successfully implant

in the womb, pregnancies often end in miscarriages" (Pennisi and Vogel (2000), page 1722, col. 1, parag. 3, lines 16-18). As the authors state, establishing pregnancies is only part of the problem and is not a guarantee of a cloned mammal being produced (Pennisi and Vogel (2000), page 1726, col. 2, lines 9-11). Thus, at the time of filing, there appears to be such unpredictability that only the cloning of nonprimate mammals was predictable. With particular regards to primates two cloned monkeys were produced, but there have been no subsequent successes in primate cloning (Pennisi and Vogel (2000), page 1726, col. 2, line 6 to col. 3, line 3). In this regard, is a post-filing report in 2002 that the cloning of monkeys, a primate, by nuclear transfer had been successful when embryonic cells were the nuclear donor, not when somatic cells were used as nuclear donor (Mitalipov, abstract). Fourteen somatic cell NT embryos were transferred to 3 recipients (Mitalipov, page 1371, col. 1, parag. 1, lines 5-7). Mitalipov states that nuclear reprogramming is a limiting parameter in monkey somatic cell cloning (page 1371, col. 1, parag. 2, lines 13-25). Mitalipov further states, clearly, that somatic cell cloning has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag, 3, lines 1-3). Thus, the art at the time of filing clearly indicates that full breadth of the claimed invention was not enabled. Thus, the skilled artisan would have needed to conduct an undue amount of experimentation without a predictable degree of success to implement the claimed invention for its entire breadth.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-18 and 20-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25-27 each state "obtained according to the method," however there is no antecedent basis for "the method." Applicant should amend the claims to state "a method."

Claim 27 is unclear because the oocyte, the cell and the offspring are each "mammalian." The preamble states "nonhuman transgenic offspring," which broadens the scope of the claim. Applicant should insert "mammal" after nonhuman.

Claims 1, 10, 20 and 25-28 state "recently expelled." However, the metes and bounds of "recently" are not clear and a definition of the term is not provided in the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-27 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by from the sheep embryos, sheep fetuses and live-born sheep of Schnieke. Schnieke et al. Science, 1997, Vol. 278, pp. 2130-2133.

Schnieke teaches the production of transgenic sheep comprising a DNA sequence encoding factor IX by nuclear transfer where the donor cell was a fibroblast transfected with the DNA sequence (page 2130, col. 3, parag. 3 to page 2131, col. 2, lines 6 and page 2131, col. 3, parag. 1 and 2). Schnieke teaches that transgenic embryos and fetuses were produced by the method (page 2131, Table 1). There is no evidence that the method of making the claimed products alters them such that they can be distinguished

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently

possess the characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). The PTO does not have the means to determine if the presently claimed nonhuman transgenic embryo, transgenic fetus or transgenic offspring are identical to those disclosed in Schnieke.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-38 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent 6,580,017 B1 issued June 17, 2003 (Echelard).

Echelard teaches methods for the production of reconstructed goat oocytes, reconstituted goat embryos, methods fro the production of transgenic goat embryos, a method of cloning a goat, methods for producing transgenic goat embryos, and methods of cloning a goat comprising incubating goat oocytes to telophase II, and then further incubating the oocyte in the presence of cytochalasin B, enucleating the activated, telophase II oocyte by aspiration or microsurgery removing second polar body and surrounding cytoplasm (col. 19, lines 6-14, and 18-26), transferring a cultured goat fetal fibroblast which contains a DNA sequence encoding antithrombin III (col. 16, lines 19-25 and lines 42-44) into the perivitiline space of the enucleated oocyte (col. 19, lines 35-40), fusing the

reconstructed oocyte by electrofusion (col. 19, lines 48-52), culturing the reconstituted oocyte to produce an transgenic embryo (col. 21, lines 22-24), which is then transferred to a surrogate mother goat to produce a transgenic goat offspring (col. 21, lines 25-27 and col. 22, line 52). Echelard teaches activation by electrofusion, ethanol, ionophore or serum (col. 13, lines 40-43 and col. 15, 15-20). Echelard also teaches the fibroblast donor cells were inherently in on of G0, G1, S, G2 or M as these are all the stages of the cell cycle. Further, Echelard teaches transgenic goat embryos, fetuses and offspring. Thus, Echelard clearly anticipates the claimed invention.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). The PTO does not have the means to determine if the presently claimed nonhuman transgenic embryo, transgenic fetus or transgenic offspring, claims 25-27, are identical to those disclosed in Echelard.

Applicant argues that Echelard teaching negative results in nuclear transfer methods where oocytes treated with ethanol in telophase failed to give viable embryos and fetuses (col. 22, lines 34 and 35). Applicant argues that Echelard does not teach or suggest enucleation of activated oocytes performed precisely when undergoing expulsion of the second polar body or after the second polar body has been expelled by the oocyte. These arguments are not persuasive.

In the specific example, ethanol treated oocytes did not yield live born goats. However, ethanol was used to activate in vivo matured oocytes that arrested prior to second polar body formation/extrusion. There is no evidence in Echelard that if immature oocytes were activated at MII with ethanol that live births would not have occurred. The present specification supports this later theory. The present specification activates MII oocytes, first polar body containing, with ethanol and permits them to continue to telophase II (page 9, step 1). Thus, Echelard's disclosure of ethanol treatment as an activating agent is enabled. Table 2 clearly shows that telophase enucleated oocytes yield a twin pregnancy and the birth of 2 live-born kids.

An oocyte in telophase is inherently activated, that is the telophase oocyte is in the process of extruding its second polar body. Thus the oocytes of Echelard are activated. Further, Echelard teaches "... oocytes which demonstrate a protrusion in the plasma membrane, usually with a spindle abutted to it, up to extrusion of the second polar body are considered to be oocytes in telophase" (col. 14, lines 32-35). Thus, Echelard teaches a range of times for enucleation which encompass the precisely when the oocyte is undergoing expulsion of the second polar body. Thus Echelard teaches enucleation precisely when the oocyte is undergoing expulsion of the second polar body. In addition, Echelard specifically teaches enucleation of telophase II oocytes by aspirating the extruded second polar body (telophase spindle) (col. 19, lines 21-25). Thus, Echelard does teach both enucleation of activated oocytes precisely when undergoing expulsion of the second polar body or after the second polar body had been expelled.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention

was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-24 and 28-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36 in view of Schnieke et al. Science, 1997, Vol. 278, pp. 2130-2133.

Bordignon teaches methods of preparing a reconstituted bovine oocyte and methods of reconstituting a bovine embryo by permitting the oocyte to mature to telophase II where there is at extrusion of the second polar body (pages 31-32, bridg. sent.), enucleating the telophase II oocyte, in the presence of cytochalasin B, by removing the second polar body and a portion of the surrounding cytoplasm using a micropipette (microsurgery) (page 32, col. 1, lines 2-5), electro-fusing a blastomere isolated from an IVF 5.5 day blastocyst to introduce a germinal cell nucleus into the enucleated oocyte (page 31, col. 1, parag. 2, lines 15-21 and page 32, col. 1, lines 5-9), and culturing in vitro the reconstructed embryo into a blastocyst (page 32, col. 1, lines 9-14). Ooctyes were in vitro matured MII oocytes, activated with ethanol or temperature variation and cultured to second polar body formation (page 30, col. 2, parag. 1).

Schnieke teaches the production of transgenic sheep comprising a DNA sequence encoding factor IX by nuclear transfer where the donor cell was a fibroblast transfected with the DNA sequence (page 2130, col. 3, parag. 3 to page 2131, col. 2, lines 6 and page 2131, col. 3, parag. 1 and 2). The fibroblasts are would be in a stage of active cellular division, G1, S, G2 or M stage. Schnieke teaches that transgenic embryos and fetuses were produced by the method (page 2131, Table 1).

Motivation for using enucleated telophase oocytes is found in Bordignon stating that the telophase approach reduces the amount of ooplasm that needs to be removed in the enucleation procedure (page 34, col. 2, parag. 2, line 13 to page 35, col. 1, line 1) and that UV irradiation and Hoechst 33342 staining are not needed (page 35, col. 1, lines 1-4), both

of which are associated with developmental deficiencies (page 35, col. 1, lines 4-8). Bordignon further states that oocyte activation can readily be determined by observation of an extruding second polar body (page 35, col. 1, lines 12-15). Schnieke offers motivation in stating that transgenesis by nuclear transfer is more efficient because transfected cells can be analyzed prior to nuclear transfer, the problem of delayed integration of the transgene into the embryonic genome is obviated and the sex of the transgenic animal can be predetermined (page 2133, col. 1, lines 3-5; parag. 2; and parag. 3, lines 1-6).

Thus at the time of filing, it would have been obvious to the ordinary artisan to produced reconstructed nonhuman mammalian oocytes, a reconstructed nonhuman mammalian embryo, and nonhuman mammal by nuclear transfer using an enucleated telophase II oocyte as recipient cell and a transfected cell as nuclear donor given the teachings of Bordignon in view of Schnieke. The cited prior art provides the requisite teaching, suggestion and motivation to reach the invention of the claims.

Applicant argues that the art did not believe prior to their invention that an oocyte could not be activated before enucleation and receive nuclei from cultured cells. Applicant refers to their specification. However, this argument is not sufficient. The present specification (page 5, lines 1-5) cites two references, which enucleated prior to activation. There is no evidence that either of these references or the art as a whole believed that activation could not occur prior to enucleation. In particular Bordignon discloses activation of oocytes prior to enucleation as telophase nuclei are activated. Applicant further argues that neither reference Bordignon nor Cibelli suggest that a host oocyte maybe be activated prior to enucleation and that neither reference teaches enucleating the activated oocyte while the oocyte is undergoing expulsion of a second polar body or has expelled a second polar body. Bordignon teaches both of these: activating an oocyte prior to enucleation and enucleating an oocyte that is has expelled a second polar body. There is no evidence that an

enucleated telophase oocyte, taught by Bordignon to yield live-born bovines in a nuclear transfer method using blastomeres as nuclear donors, would not be reasonably expected to yield a live-born nonhuman mammal when a transfected cell was used as nuclear donor.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

February 12, 2005